II. NON-TECHNICAL ABSTRACT:

The prostate has become the leading site of internal malignancy in men. Prostate cancer is responsible for approximately 3% of all deaths in men over the age of 55, an estimated 40,400 in 1995. The incidence and mortality rates are higher in African American men than in any population in the world. Since prostate increases more rapidly with age than any other tumor and the average age of American men is increasing, the number of patients with prostate cancer and the number of deaths from the disease are expected to rise steadily into the next century.

Current therapies for localized prostate cancer include surgical removal of the prostate (radical prostatectomy) or local radiation. Failure after radiation has been estimated to occur in the majority of patients as determined by a rising serum (Prostate Specific Antigen) PSA >5 years after therapy. Patients who have locally recurrent prostate cancer after definitive radiation therapy do not have any standard therapeutic procedure which has been shown to have a high degree of efficacy in eradicating the tumor with a reasonable degree of safety. Thus, the potential risks associated with the use of gene therapy in this group would appear reasonable. We specifically selected this group of patients to test the safety and therapeutic effects of this gene therapy approach because of the lack of standard alternative forms of curative therapy, the high risk associated with either salvage radical prostatectomy or salvage radiation therapy with interstitial implants, because of the poorly documented efficacy and toxicity of cryotherapy, and because of the known lack of permanent cancer control associated with androgen ablation therapy. Consequently, we believe the risk associated with this gene therapy approach in these patients is offset by the potential significant therapeutic benefit of reducing or possibly eliminating the cancer.

Direct introduction of therapeutic genes into tumor cells may provide an effective treatment of prostate tumors. One strategy is to confer drug sensitivity to tumor cells by inserting a recombinant gene into them. This gene is from the common Herpes virus and codes for the enzyme thymidine kinase (HSV-tk). Thymidine kinase converts the anti-viral drug ganciclovir into a form that is toxic to rapidly dividing cells such as tumor cells. Non-dividing cells are not harmed. This approach is especially suitable for the treatment of prostate tumors since the normal prostate tissue is made up largely of non-dividing cells. Several techniques have been used to introduce therapeutic genes into tumors. Of these, virus-mediated transfer is currently the most efficient method and the most efficient virus is the genetically engineered adenovirus. We have demonstrated using human and animal models for prostate cancer that adenovirus-mediated transfer of the HSV-tk gene resulted in sensitivity to ganciclovir of all cell lines tested in *vitro* and growth suppression of mouse prostate tumors *in vivo*.

This phase I study is designed to study the safety and efficacy of gene therapy for patients with local recurrence of prostate cancer after radiation therapy. These patients do not have any standard therapeutic procedure which has been shown to have a high degree of efficacy in eradicating the tumor at a reasonable degree of safety. Thus, the potential risks associated with the use of gene therapy in this group would appear reasonable. Patients with radiation recurrent prostate cancer will be treated with intra-tumor injection of a replication-defective adenovirus vector delivering the HSV-tk gene. Initial tests will use a low dose of virus. Ganciclovir will then be administered intravenously at 5 mg/kg/day for 14 days. Only one course of therapy will be administered. Each patient will be carefully monitored for adverse effects. Five patients will be tested with this low dose before another group of patients is treated with a higher dose and monitored closely for 1 month. This will be repeated until the target dose is reached or significant toxicity is detected. Effectiveness will be monitored by serial measurements of serum PSA, digital rectal exam, transrectal ultrasound of the prostate, prostate biopsy and by comparing survival times to historical survival times for patients with radiation recurrent prostate tumors. The primary objective of this initial study is to determine whether the treatment is associated with significant toxicity.